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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,732	12/26/2006	Claudia Magagnoli	PP021455.0004 (2300-21455	5728

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EXAMINER	
GRASER, JENNIFER E	
ART UNIT	**PAPER NUMBER**
1645	

MAIL DATE	DELIVERY MODE
05/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,732	MAGAGNOLI ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,5,10,12, 14, 15, 18, 23, 25, 27-45, 47 and 48* is/are pending in the application.

4a) Of the above claim(s) *15,18,23,25,27-42,47 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,10,12,14 and 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/22/10 has been entered.

Claims 1, 5, 10, 12, 14, and 43-45 are currently under examination.

Claims 15, 18, 23, 25, 27-42, 47 and 48 are withdrawn from consideration as they were previously withdrawn for being drawn to a non-elected invention.

Applicant's reply has overcome the following rejection(s): rejection of claims 1, 2, 6-8, 12-14 and 43-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Pizza et al (US-A-2002/0044939) and rejection of claims 1, 2, 6-8, 12-14, and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Pronk et al (J.Biochem.Chem. 1985.260(25): 13580-13584); Pizza is silent as to both charged amino acids and zwitterionic detergents, as claimed . Pronk does not teach compositions comprising an LT or CT protein, a charged amino acid and a zwitterionic detergent.

Claim Rejections - 35 USC § 112-Scope of Enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 5, 10, 12, 14 and 43-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "a composition comprising an isolated LTK63 or LTK72 protein or AB5 E.coli heat labile toxin (LT), arginine phosphate in an amount of from about 100mM to about 400mM, and CHAPS (3-(3-Cholamidopropyl)-dimethylammonio-1-propanesulfonate) in an amount of from about 0.05% to about 0.5% by weight per volume (w/v)", does not reasonably provide enablement for compositions comprising *any* AB5 cholera toxin (CT) ADP-ribosylating toxin with any amount of arginine phosphate and CHAPS or LTK63 or LTK72 of LT with any amount of CHAPS or arginine phosphate. The specification is also not enabled for wild-type or non-attenuated LT toxin in the immunogenic compositions of claims 43-45. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification has demonstrated that the particular agents, arginine phosphated and CHAPS work to greatly stabilize the LTK63 protein. The specification has not demonstrated that said agents would be effective in stabilizing any other bARE class protein. The instant specification fails to enable any other composition with an effective stabilizing agent. The prior art (see Wang, W. International J. Pharmaceutics, 199, 185: 129-188; e.g., 'Conclusions') teaches that the stabilization of polypeptides in pharmaceutical areas is unpredictable and that trials and errors play major roles in finding an effective combination. The art is highly unpredictable. Accordingly, the specification does not encompass the scope of these claims. It is unclear what

structure is encompassed by an 'analog' of any charged or uncharged amino acid. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

The specification teaches that there was a long felt need in the art for a suitable means to stabilize the bARE class proteins. There is established unpredictability among agents. The specification at page 21 teaches that there are some confilicting reports on the benefits of an amorphous excipient in terms of stabilization and that some studies have shown that the addition of amorphous exoipients to protein solutions can actually destabilise a protein through interactions between the excipient and the protein (see for example, Pike et a@ Biopharm 1990 3:2629 and WO01/41800). The specification states that zwittergents, such as CHAPS, are advantageous because they are less denaturing than the Zwittergent® 3-X series, possibly owing to their rind steroid ring structure. Thus, zwittergents, such as CHAPS, may enhance the stable association

of the A and B subunits. The specification at the bottom of page 24 teaches that the identification of charged Arginine as a stabilizing agent is unexpected.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidancepresented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to the ability of other amino acids, proteins and zwitteronic detergents and their ability to provide a stabilized protein 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). With regard to (4) the nature of the invention and (5) the state of the prior art, these have been discussed in the previous Office Actions.

Given the lack of guidance contained in the specification, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Applicants argue that, noting the well-characterized nature of CT and LT

endotoxins and that these two proteins are "structurally, functionally and immunologically" similar and that LT and CT are immunologically cross-reactive. They argue that the skilled artisan would know that any LT or CT protein could be used in the claimed compositions. These arguments have been fully and carefully considered but are not deemed persuasive. CT and LT are not identical proteins. The stabilization of any given protein is unpredictable. While it is reasonable to extrapolate the stability of the LTK63 to an LTK72 or native LT protein, absent working examples, utilizing a completely different protein, e.g., any CT protein, one of th skill in the art would not be enabled. Tsumoto et al. (Biotechol. Prog. 2004, 20: 1301-1308; published online 9/11/04) teaches that to facilitate refolding of recombinant proteins form inclusion bodies, 0.1 to 1 M arginine is customarily included in solvents used for refolding the proteins by dialysis or dilution. It is taught that arginine can suppress protein aggregation but little is known about the mechanism. Page 1302 column 1, teaches that it cannot be explained why arginine does not work for certain proteins. The examples set forth in the instant specification have only shown that the specific combination of mutant LT, CHAPS and arginine phosphate have enhanced stability, with the effective amount of Arginine phosphated between about 100mM to about 400mM and CHAPS from about 0.05% to about 0.5% (w/v). LT K63 instability is dependent on two different phenomena: crystallization/precipitation and dissociation. Athough CHAPS is unable to prevent LT K63 precipitation at high LT K63 concentration (about 2mg/ml), no dissociating effect has been observed. L-Arginine prevents protein precipitation at a very high LT K63 concentration (about 17mg/ml) but L-Arginine may

have an effect on AB5 dissociation. The use of a combination of CHAPS and L-Arginine appears to provide a synergistic effect in terms of preventing both LTK63 precipitation and dissociation over time. In particular, stability experiments to determine the optimal L-arginine (100-200 mM) and CHAPS (0.05 - 0.25%) concentration, when used in combination, have shown that positive results in terms of stability were obtained after 3 month The top of page 81 of the instant specification teaches that CHAPS and L-arginine were selected to synergistically stabilize the LT K63 protein, e.g., by preventing both precipitation and dissociation over time. It is noted that one would not use a non-mutant LT or CT toxin in an 'immunogenic composition' as claimed in instant claims 43-45. Applicants arguments were addressed in the body of the rejection recited above.

Prior art Made of Record:

Ryu et al (Biotech. Bioprocess Eng. 1998, 3:32-34). The reference teaches that L-arginine remarkably increases the thermal stability of *Aspergillus* phytase in an aqueous solution. Page 33, column 2, teaches that L-arginine has bee used as a unique additive for the stabilization of tissue plasminogen activator in a liquid dosage formation and prevented the cleavage of peptide bonds.PAge 34 teaches that L-arginine has been known to bind to some regions of protein via ionic interaction with concomittant stabilization of protein structure.

Strub et al (BMC Biochem. 2004.; published online July 13, 2004. 5: 9). The reference teaches mutation of exposed hydrophobic amino acids to arginine increase protein stability. The reference teaches replacing 14 solvent-exposed hydrophobic

residues of acetylcholinesterase by arginine. Half of the resultant mutants showed an increased stability.

Tsumoto et al. (Biotechol. Prog. 2004, 20: 1301-1308; published online 9/11/04). The refernces teaches that to facilitate refolding of recombinant proteins form inclusion bodies, 0.1 to 1 M arginine is customarily included in solvents used for refolding the proteins by dialysis or dilution. It is taught that arginine can suppress protein aggregation but little is known about the mechanism. Page 1302 column 1, teaches that it cannot be explained why arginine does not work for certain proteins.

Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645

5/13/10